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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/527,931	08/26/2005	Adrian Bot	8114-008-WO-US	7472

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EXAMINER	
WEHBE, ANNE MARIE SABRINA	
ART UNIT	**PAPER NUMBER**
1633	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/527,931	BOT ET AL.	
	Examiner	Art Unit	
	Anne Marie S. Wehbe	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 November 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-36* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *Notice to Comply*.

DETAILED ACTION

Applicant's response to the restriction/election requirement received on 11/5/07 has been entered. Applicant's election with traverse of the species a) pA:pU as the species of dsRNA and the species m) Her-2 as the species of antigenic peptide is acknowledged. The traversal is on the grounds that there would be no burden on the examiner to search all the species together since in applicant's opinion the search for each species would be largely coextensive. In response, it is first noted that the election requirement between the various species of peptide epitopes present in the Ig backbone is withdrawn upon further consideration by the examiner. However, applicant's traversal of the election requirement between various species of dsRNA is not found persuasive. The requirement for species election between species of dsRNA was applied because the species listed lack the same or corresponding special technical feature as set forth under PCT Rule 13.2 since each molecule is materially different in physical, chemical, and functional properties. Further, it is noted that there is an examination and search burden for these patentably distinct species due to their mutually exclusive characteristics. The species require a different field of search (e.g., searching different electronic resources, or employing different search queries); and/or the prior art applicable to one species would not likely be applicable to another species; and/or the species are likely to raise different non-prior art issues under 35 U.S.C. 101 and/or 35 U.S.C. 112, first paragraph. As such, a serious burden does exist such that the election requirement between the various species of dsRNA is deemed proper and made FINAL.

Claims 1-36 are currently pending and under consideration based on the elected species of pA:pU.

Nucleotide and/or Amino Acid Sequences

This application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. This application contains numerous sequences encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821 (a)(1) and (a)(2). However, no sequence listing in either paper form or CRF, nor the required statement that the contents of the paper and CRF listings are identical as required under 37 CFR 1.821 through 1.825 are present in the instant application.

It is further noted that while many of the sequences set forth in the specification and Figures are identified by SEQ ID NOS, a number are not so identified. Specifically, Figures 1F, 1H, 1L, and 1M contain sequences encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821 (a)(1) and (a)(2) which are not identified by a SEQ ID NO. It is further noted that the brief description of these Figures in the specification also not identify the sequences by SEQ ID NO. In addition, at least pages 36-37, 39-40 and 56 also contain sequences encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821 (a)(1) and (a)(2) which are not identified by a SEQ ID NO. Please note that compliance to 37 CFR 1.821-1.825 requires that each recitation of a sequence be followed by the appropriate SEQ ID NO. Applicant is encouraged to perform a thorough review of the Figures and specification to identify all sequences meeting the definitions under 37 CFR 1.821(a) which require SEQ ID NOS.

Please note that a response to this office action which does not place this application in compliance with 37 CFR 1.821-1.825 will be considered non-responsive.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-36 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for 1) methods of generating an enhanced CD4+ T helper cell response in a patient comprising administering to the patient an immunoglobulin comprising an antigenic peptide epitope and the dsRNA pA:U, wherein the T helper response comprises enhanced Th1 and Th2 responses, and 2) methods of generating an enhanced Influenza NP specific CD8+ T cell response in a patient comprising administering to the patient by subcutaneous injection a portion of an immunoglobulin comprising a heavy chain containing an Influenza NP CTL epitope replacing the V and CH1 regions, wherein the Ig-peptide is not an immune complex or receptor cross-linking antibody, and pA:U, wherein both Tc1 and Tc2 type CD8+ T cells are induced, does not reasonably provide enablement for generating CD8+ T cells responses using any immunoglobulin comprising a peptide epitope. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The specification broadly teaches the induction of T cell responses by co-administration of a peptide epitope comprised in an immunoglobulin backbone and a dsRNA such as pA:U. The specification teaches that the inclusion of T helper or cytotoxic epitopes within the CDR regions of an immunoglobulin allows for Fc receptor mediated endocytosis of the antigenized immunoglobulin followed by processing and presentation of the helper T cell or cytotoxic T cell epitopes in the context of MHC class II or I respectively. While the use of antigenized immunoglobulin to deliver various viral or bacterial peptides to the class II pathway in antigen presenting cells was known at the time of filing, the prior art teaches that immunoglobulin molecules modified to comprise cytotoxic T cell peptide epitopes within a CDR where incapable of efficiently loading MHC class I molecules following FcR mediated endocytosis and were not able to stimulate peptide specific CTL. For example, Bona et al. teaches that while antigen presenting cells transfected with DNA encoding an antigenized immunoglobulin comprising a cytotoxic T cell Influenza NP epitope can present the NP peptide in the context of MHC class I and stimulate peptide specific CTL responses, treating the antigen presenting cells with exogenous Ig-NP did not result in any NP specific CTL activity (Bona et al. (US Patent No. 5,969,109, 1999), column 25). Zaghouani et al. also shows that contact of antigen presenting cells with soluble Ig-NP does not result in the generation of NP peptide-MHC class I complexes and that the treated APCs do not stimulate NP specific CTL (Zaghouani et al. (1993) Eur. J. Immunol., Vol. 23, 2746-2750, see page 2749). Zaghouani et al. teaches that peptides generated from the soluble Ig-NP in the endocytic compartment are excluded from presentation on MHC class I (Zaghouani et al., page 2749, column 1). Zanetti et al. as well failed to stimulate CTL using immunoglobulin containing an NP epitope (Zanetti et al. (WO 94/28026, 1994), page 39).

Thus, at the time of filing, the prior art provides strong evidence that antigenized immunoglobulin comprising CTL epitopes are not presented by MHC class I.

The specification provides specific evidence that a single immunoglobulin molecule comprising an Influenza NP CTL epitope inserted in place of the V and CH1 regions of a heavy chain immunoglobulin molecule, where the immunoglobulin does not form an immune complex or induce Fc receptor cross-linking, is capable of being taken up by antigen presenting cells and processed for presentation by MHC class I, and is further capable of stimulating Tc2 type CD8+ T cells. The specification further teaches that addition of the dsRNA pA:U results in the stimulation of both Tc1 and Tc2 type CD8+ T cells and the observation of NP peptide specific cytolytic activity. In view of the previous failure by several researchers to generate using antigenized immunoglobulin, applicant's success appears to be based on the specific structure and properties of the NP-Ig used by applicants both alone and in combination with pA:U. Thus, the specific structural features of the NP-Ig used by applicants is essential to the successful practice of the methods as claimed as other antigenized immunoglobulin encompassed by the claims have been clearly demonstrated to be incapable of loading MHC class I molecules following FcR mediated endocytosis. Further, the working example is limited to the demonstration that a single dsRNA, pA:U can modulate the ability of the NP-Ig to stimulate not only Tc2 type CD8+ T cells, but Tc1 type CD8+ T cells as well resulting in an observed cytotoxic T cell response. As such, based on the state of the prior art, the breadth of the claims, and applicant's single example of an NP-Ig capable of loading MHC class I and stimulating CD8+ T cells, and the single example of a combination of NP-Ig and pA:U dsRNA capable of stimulating cytotoxic T cells, it would have been considered unpredictable by the skilled artisan

at the time of filing to use any antigenized immunoglobulin alone or in combination with pA:U to load MHC class I molecules on antigen presenting cells or to stimulate CD8+ T cells.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 13-29 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 13 recites, " [a] method of loading an antigen presenting cells and generating an immune response to an antigen in a patient by use at least one peptide epitope attached to an immunoglobulin or portion thereof thereby forming an Ig-peptide complex wherein when the Ig-peptide complex is administered to a patient in vivo in conjunction with dsRNA ....." (emphasis added by examiner). The claim as written lacks any particular method steps. The phrase "by use" does not set forth any specific step to be followed. Further, the phrase "wherein when" is a conditional phrase such that it is unclear whether the steps recited following this clause are specifically intended to be part of the method as claimed, or whether these steps are simply intended to describe a particular property of the Ig-peptide complex recited in the claims. Thus, the metes and bounds of the claimed method cannot be determined. As such, claim 13 provides for the use of an Ig-peptide complex, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how

this use is actually practiced. Claims 14-29 depend on claim 13 and therefore are included in this rejection.

Claims 13-29 are further rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Claim Rejections - 35 USC § 103

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later

invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-4, 6-7, 9-12, 30-32, and 34-36 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent No. 5,969,109 (1999), hereafter referred to as Bona et al., in view of US Patent No. 3,906,092 (1975), hereafter referred to as Hilleman et al., and Cella et al. (1999) J. Exp. Med., Vol. 189 (5), 821-829.

Bona et al. teaches methods of enhancing the cellular and humoral immune response to an antigen by administering a chimeric antibody comprising one or more viral T helper and/or B cell epitopes to a mammal (Bona et al., columns 20-22). Bona et al. further teaches that the T and/or B cell epitopes are covalently attached to the immunoglobulin by being inserted into one or more of the CDRs of the variable region of the immunoglobulin (Bona et al., columns 18-19). Bona et al. also teaches that the epitopes are derived from viruses such as RSV, HIV, Hepatitis B, and Influenza or are a tetanus toxoid T helper epitope (Bona et al., columns 9-10, and 19). In addition, Bona et al. teaches that an immunoglobulin containing an Influenza HA helper T cell peptide epitope in CDR3 was capable of stimulating HA specific CD4+ helper T cells *in vitro* or *in vivo* following subcutaneous administration of the Ig-HA in CFA (Bona et al., columns 7 and 32).

Bona et al. differs from the present invention by failing to teach the co-administration of dsRNA with the antigenized immunoglobulin. Hilleman et al. supplements Bona et al. by teaching that immune responses to antigen in adjuvant can be enhanced by the inclusion of dsRNA, such as poly A:U (Hilleman et al., columns 2, 4, and 15-18). While Hilleman et al.

focuses on the enhancement of antibody responses by dsRNA, Cella et al. supplements both Bona et al. and Hilleman et al. by teaching that dsRNA upregulates MHC class II expression on immature dendritic cells and induces their maturation (Cella et al., page 825). Cella et al. further teaches that dendritic cells matured with dsRNA exhibit increased capacity to prime and polarize T cells (Cella et al., page 826). Therefore, in view of the specific motivation to combine adjuvanated antigens with dsRNA such as poly A:U in order to increase immune responses taught by Hilleman et al. and the further teachings of Cella et al. regarding the effects of dsRNA in increasing MHC class II expression and enhancing the capacity of dendritic cells to prime T cells, it would have been *prima facie* obvious to the skilled artisan at the time of filing to combine a dsRNA such as poly A:U with the antigenized immunoglobulins comprising T helper peptide epitopes taught by Bona et al. in order to enhance the formation of peptide-MHC class II complexes on antigen presenting cells and the induction of peptide specific T helper responses. Further, in view of the successful generation of peptide specific T helper responses using antigenized immunoglobulins taught by Bona et al, and the evidence for increased expression of MHC class II on antigen presenting cells such as dendritic cells following exposure to dsRNA, the skilled artisan at the time of filing would have had a reasonable expectation of success in enhancing immune responses to an antigen in a patient by administering a immunoglobulin comprising a T helper peptide epitope in conjunction with the dsRNA poly A:U.

No claims are allowed.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Wehbé, Ph.D., whose telephone number is (571) 272-0737. If the examiner is not available, the examiner's supervisor, Joseph Woitach, can be reached at (571) 272-0739. For all official communications, **the new technology center fax number is (571) 273-8300**. Please note that all official communications and responses sent by fax must be directed to the technology center fax number. For informal, non-official communications only, the examiner's direct fax number is (571) 273-0737. For any inquiry of a general nature, please call (571) 272-0547.

The applicant can also consult the USPTO's Patent Application Information Retrieval system (PAIR) on the internet for patent application status and history information, and for electronic images of applications. For questions or problems related to PAIR, please call the USPTO Patent Electronic Business Center (Patent EBC) toll free at 1-866-217-9197. Representatives are available daily from 6am to midnight (EST). When calling please have your application serial number or patent number available. For all other customer support, please call the USPTO call center (UCC) at 1-800-786-9199.

Dr. A.M.S. Wehbé

/Anne Marie S. Wehbé/
Primary Examiner, A.U. 1633

Application No.: 10/527,931

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

- [X] 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to these regulations, published at 1114 OG 29, May 15, 1990 and at 55 FR 18230, May 1, 1990.
- [X] 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).
- [X] 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).
- [ ] 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."
- [ ] 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).
- [ ] 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).
- [X] 7. Other: Numerous sequences present in the Figures and specification are not identified by SEQ ID NOS.

Applicant Must Provide:

- [X] An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".
- [X] An initial or substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification.
- [X] A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (703) 308-4216
For CRF Submission Help, call (703) 308-4212
For PatentIn software help, call (703) 308-6856

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